

**What is claimed is:**

- 10 1. A dosage form of combination of high dose high solubility active ingredient, as modified release and low dose active ingredient as immediate release suitable for swallowing; comprising of dual retard technique to control the release of high dose, high solubility active ingredient, wherein said dosage form comprising of an  
15 inner portion having a low dose active ingredient as immediate release and an outer portion having a high dose, high solubility active ingredient as modified release, in which the outer portion comprises a) micro matrix particles and b) coating on micro matrix  
20 particles.
2. A dosage form according to claim 1, in the form of a tablet, wherein said inner portion is covered by the outer portion from all the sides except top surface that remains uncovered.
- 25 3. A dosage form according to claim 1, wherein the dosage form is with sufficient reduction in the amount of release controlling agent.
4. A dosage form according to claim 1, wherein the micro matrix particles comprises one or more hydrophobic  
30 release controlling agents.
5. A dosage form according to claim 4, wherein the hydrophobic release controlling agents are selected from the group comprising of ammonio methacrylate copolymers type A and B as described in USP, methacrylic acid

5 copolymer type A, B and C as described in USP,  
polyacrylate dispersion 30% as described in Ph. Eur.,  
polyvinyl acetate dispersion, ethylcellulose, cellulose  
acetate, cellulose propionate (lower, medium or higher  
molecular weight), cellulose acetate propionate,  
10 cellulose acetate butyrate, cellulose acetate phthalate,  
cellulose triacetate, poly(methyl methacrylate),  
poly(ethyl methacrylate), poly(butyl methacrylate),  
poly(isobutyl methacrylate), poly (hexyl methacrylate),  
poly(isodecyl methacrylate), poly (lauryl methacrylate),  
15 poly(phenyl methacrylate), poly (methyl acrylate), poly  
(isopropyl acrylate), poly (isobutyl actylate), poly  
(octadecyl acrylate), waxes such as beeswax, carnauba  
wax, microcrystalline wax, and ozokerite; fatty alcohols  
such as cetostearyl alcohol, stearyl alcohol; cetyl

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alcohol and myristyl alcohol; and fatty acid esters such  
as glyceryl monostearate, glycerol distearate, glycerol  
monooleate, acetylated monoglycerides, tristearin,  
tripalmitin, cetyl esters wax, glyceryl palmitostearate,  
25 glyceryl behenate and hydrogenated castor oil.

6. A dosage form according to claim 5, wherein the  
hydrophobic release controlling agent(s) is selected  
preferably from ammonio methacrylate co-polymers.

7. A dosage form according to claim 6, wherein the preferred  
30 ammonio methacrylate co-polymers are selected from  
Eudragit RSPO (Ammonio Methacrylate Copolymer type B  
USP), Eudragit RL (Ammonio Methacrylate Copolymer type A  
USP) and Eudragit NE30D (Polyacrylate dispersion 30% Ph.  
Eur.).

- 5 8. A dosage form according to claim 1, wherein in micro  
matrix particles, the active ingredient and one or more  
hydrophobic release controlling agents are present in a  
ratio of from 100:1 to 100:75.
9. A dosage form according to claim 8, wherein in micro  
10 matrix particles, the active ingredient and one or more  
hydrophobic release controlling agents are present  
preferably in ratio of from 100:2.5 to 100:50.
10. A dosage form according to claim 8, wherein in micro  
matrix particles, the active ingredient and one or more  
15 hydrophobic release controlling agents are present more  
preferably in ratio of from 100:2.5 to 100:30
11. A dosage form according to claim 8, wherein in micro  
matrix particles, the active ingredient and one or more  
hydrophobic release controlling agents are present most  
20 preferably in ratio of from 100:2.5 to 100:20.
12. A dosage form according to claim 1, coating of micro  
matrix particles comprises one or more hydrophobic  
release controlling agents.
13. A dosage form according to claim 12, wherein the  
25 hydrophobic release controlling agents are selected  
from the group comprising of ammonio methacrylate  
copolymers type A and B as described in USP, methacrylic  
acid copolymer type A, B and C as described in USP,  
polyacrylate dispersion 30% as described in Ph. Eur.,  
30 polyvinyl acetate dispersion, ethylcellulose, cellulose  
acetate, cellulose propionate (lower, medium or higher  
molecular weight), cellulose acetate propionate,  
cellulose acetate butyrate, cellulose acetate phthalate,  
cellulose triacetate, poly(methyl methacrylate),

5 poly(ethyl methacrylate), poly(butyl methacrylate),  
poly(isobutyl methacrylate), poly (hexyl methacrylate),  
poly(isodecyl methacrylate), poly (lauryl methacrylate),  
poly(phenyl methacrylate), poly (methyl acrylate), poly  
(isopropyl acrylate), poly (isobutyl actylate), poly  
10 (octadecyl acrylate), waxes such as beeswax, carnauba  
wax, microcrystalline wax, and ozokerite; fatty alcohols  
such as cetostearyl alcohol, stearyl alcohol; cetyl  
alcohol and myristyl alcohol; and fatty acid esters such  
as glyceryl monostearate, glycerol distearate, glycerol  
15 monooleate, acetylated monoglycerides, tristearin,  
tripalmitin, cetyl esters wax, glyceryl palmitostearate,  
glyceryl behenate glycerol distearate, and hydrogenated  
castor oil.

14.A dosage form according to claim 13, wherein the  
20 hydrophobic release controlling agent(s) is selected  
from fatty acid esters.

15.A dosage form according to claim 14, wherein the  
hydrophobic release controlling agents is selected from  
the group comprising of hydrogenated castor oil and  
25 glycerol distearate.

16.A dosage form according to claim 1, wherein in outer  
portion, micro matrix particles and coating of one or  
more hydrophobic release controlling agents are present  
in a ratio of from 100:0.5 to 100:75.

30 17.A dosage form according to claim 16, wherein in outer  
portion, micro matrix particles and coating of one or  
more hydrophobic release controlling agents are present  
preferably in a ratio of from 100:1 to 100:50.

- 5 18.A dosage form according to claim 16, wherein in outer  
portion, micro matrix particles and coating of one or  
more hydrophobic release controlling agents are more  
preferably present in a ratio of from 100:2.5 to 100:20.
- 10 19.A dosage form according to claim 1, wherein the weight  
ratio of immediate release active ingredient and  
modified release active ingredient is from 1:10 to  
1:15000.
- 15 20.A dosage form according to claim 1, wherein the low dose  
active ingredient comprises dose less than or equal to  
50 mg.
- 20 21.A dosage form according to claim 1, wherein the low  
dose active ingredient is selected from the group  
comprising of antidiabetic agents, anti-histamines,  
anti-depressants, anti-viral agents, anesthetics,  
antacids, anti-arththriics, antibiotics, anti-  
psychotics, anti-spasmodics, anxiolytic agents, appetite  
suppressants, cardiovascular agents, cough suppressants,  
emollients, gastro-intestinal agents, growth regulators,  
respiratory stimulants, vitamins, angiotensin converting  
25 enzyme inhibitors, anti-asthmatics, anti-  
cholesterolemics, anti-convulsants, anti-depressants,  
anti-diarrhea preparations, anti-infective, anti-  
inflammatory agents, anti-nauseants, anti-stroke agents,  
anti-tumor drugs, anti-tussives, anti-uricemic drugs,  
30 amino-acid preparations, antiemetics, antiobesity drugs,  
antiparasitics, antipyretics, appetite stimulants,  
cerebral dilators, chelating agents, cholecystokinin  
antagonists, cognition activators, deodorants,  
dermatological agents, diuretics, erythropoietic drugs,  
35 fertility agents, synthetic hormones, laxatives, mineral

5 supplements, neuroleptics, neuromuscular agents,  
peripheral vaso-dilators, prostaglandins, vaginal  
preparations, vaso-constrictors, vertigo agents,  
sulphonylurease, meglitinides, PPAR gama agonist  
[insulin sensitisers (thiazolidinedione)], PPAR alpha  
10 and gamma agonist, alpha-glucosidase inhibitors and the  
like.

22.A dosage form according to claim 21, wherein the low  
dose active ingredient is selected from the group  
comprising of zafirlukast, quinapril hydrochloride,  
15 isotretinoin, rabeprazole sodium, estradiol(e2),  
norethindrone acetate, risedronate sodium, pioglitazone  
HCl, amphetamine, anagrelide hydrochloride, biperiden  
HCl, mephalan, alprazolam, ramipril, naratriptan  
hydrochloride, leflunomide, anastrozole, exemestane,  
20 paroxetine mesylate, candesartan cilexetil, almotriptan,  
cerivastatin, betaxolol hydrochloride, bisoprolol  
fumarate, deloratadine, clonazepam, clorazepate  
dipotassium, clozapine, methylphenidate hci, carvedilol,  
warfarin sodium, norgestrel, ethinyl estradiol,  
25 cyclophosphamide, pemoline, liothyronine sodium,  
misoprostol, tolterodine tartrate, dextroamphetamine  
sulfate, dicyclomine hydrochloride, digoxin, oxybutynin  
chloride, doxazosin mesylate, ethacrynate sodium,  
venlafaxine HCl, enalapril maleate, estradiol,  
30 estropipate, famotidine, letrozole, fludrocortisone  
acetate, fluoxetine, dexmethylphenidate hci, alendronate  
sodium, ziprasidone, glipizide, glyburide, miglitol,  
guanabenz acetate, haloperidol, doxercalciferol,  
zalcitabine, hydrochlorothiazide, hydromorphone HCl,  
35 indapamide, estradiol, nitric oxide, ketorolac

5 tromethamine, clonazepam, granisetron, lamotrigine,  
 fluvastatin sodium, levonorgestrel, levothyroxine  
 sodium, atorvastatin calcium, lisinopril, minoxidil,  
 loperamide, loratidine, lorazepam, lovastatin,  
 pravastatin sodium, fluvoxamine maleate, acetaminophen,  
 10 acyclovir, aminocaproic acid, pitavastatin,  
 rosuvastatin, dalvastatin, escitalopram, sertraline, celecox  
 ib, parecoxib, valdecoxib, glibenclamide  
 (glyburide), glipizide, gliclazide, glimepiride,  
 tolazamide, tolbutamide, clorpropamide, gliquidone,  
 15 nateglinide, glyburide, glisoxepid, glibornuride,  
 phenbutamide, tolcyclamide, repaglinide, troglitazone,  
 ciglitazone, pioglitazone, englitazone, acarbose,  
 voglibose, emiglitate, miglitol, farglitazar, (S)-2-  
 ethoxy-3-[4-(2-{4-  
 20 methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid,  
 3-{4-[2-(4- tert-butoxycarbonylaminophenyl)  
 ethoxy]phenyl}-(S)-2-ethoxy propanoic acid, L-6766892  
 and pharmaceutically acceptable salts thereof.

23. A dosage form according to claim 1, wherein the high  
 25 dose, high solubility active ingredient comprises dose  
 from 500 mg to 1500 mg.

24. A dosage form according to claim 1, wherein the high  
 dose, high solubility active ingredient is selected from  
 the group comprising of antidiabetic agents, anti-  
 30 histamines, anti-depressants, anti-viral agents,  
 anesthetics, antacids, anti-arthritiics, antibiotics,  
 anti-psychotics, anti-spasmodics, anxiolytic agents,  
 appetite suppressants, cardiovascular agents, cough  
 suppressants, emollients, gastro-intestinal agents,  
 35 growth regulators, respiratory stimulants, vitamins,

5        angiotensin converting enzyme inhibitors, anti-  
asthmatics, anti-cholesterolemics, anti-convulsants,  
anti-depressants, anti-diarrhea preparations, anti-  
infective, anti-inflammatory agents, anti-nauseants,  
anti-stroke agents, anti-tumor drugs, anti-tussives,  
10        anti-uricemic drugs, amino-acid preparations,  
antiemetics, antiobesity drugs, antiparasitics,  
antipyretics, appetite stimulants, cerebral dilators,  
chelating agents, cholecystokinin antagonists, cognition  
activators, deodorants, dermatological agents,  
15        diuretics, erythropoietic drugs, fertility agents,  
synthetic hormones, laxatives, mineral supplements,  
neuroleptics, neuromuscular agents, peripheral vaso-  
dilators, prostaglandins, vaginal preparations, vaso-  
constrictors, biguanides, vertigo agents and the like.

20        25. A dosage form according to claim 1, wherein the high  
dose, high solubility active ingredient is selected from  
the group comprising of metformin hydrochloride,  
phenformin, buformin, potassium chloride, clindamycin,  
hydroxyurea, erythromycin, lactobionate, vancomycin  
25        hydrochloride, balsalazide disodium, sodium valproate,  
niacin, aminocaproic acid, acetaminophen ciprofloxacin,  
quetiapine and pharmaceutically acceptable salts  
thereof.

30        26. A dosage form according to claim 1, wherein inner  
portion may optionally contain more than one low dose  
active ingredients.

35        27. A dosage form according to claim 1, wherein the  
dissolution of high dose, high solubility active  
ingredient is not more than 45% in 1 hour and between  
25% to 90% in 6 hours.



- 5 28. A dosage form according to claim 1, wherein the dosage form can be given twice a day or more preferably can be given once a day oral formulation.
29. A dosage form according to claim 1, is used for human beings.
- 10 30. A process for the preparation of a dosage form comprising a) preparation of inner portion and b) preparation of outer portion.
31. A process for the preparation of a dosage form as claimed in claim 30, wherein preparation of outer  
15 portion comprising a) preparing a micro matrix particles containing high dose, high solubility active ingredient and one or more hydrophobic release controlling agent and b) coating the said micro matrix particles containing high solubility active ingredient and one or  
20 more hydrophobic release controlling agent.
32. A dosage form according to claim 1, wherein outer portion may optionally contain more than one high dose high solubility active ingredients.
33. A dosage form of combination of high dose high  
25 solubility antidiabetic active ingredient is as modified release and low dose antidiabetic active ingredient as immediate release, suitable for swallowing; comprising of dual retard technique to control the release of the high dose high solubility antidiabetic active ingredient  
30 wherein said dosage form comprising of an inner portion having a low dose antidiabetic active ingredient as immediate release and an outer portion having a high dose high solubility antidiabetic active ingredient as modified release, in which the outer portion comprises

5       a) micro matrix particles and b) coating on micro matrix particles.

34. A dosage form according to claim 33, which is a tablet, in which the inner portion is covered by the outer portion from all the sides except top surface that  
10       remains uncovered.

35. A dosage form according to claim 33, wherein the dosage form is with sufficient reduction in the amount of release controlling agent.

36. A dosage form according to claim 33, wherein the micro  
15       matrix particles comprises one or more hydrophobic release controlling agents.

37. A dosage form according to claim 36, wherein the hydrophobic release controlling agents are selected from the group comprising of ammonio methacrylate copolymers  
20       type A and B as described in USP, methacrylic acid copolymer type A, B and C as described in USP, polyacrylate dispersion 30% as described in Ph. Eur., polyvinyl acetate dispersion, ethylcellulose, cellulose acetate, cellulose propionate (lower, medium or higher  
25       molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, poly(methyl methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate), poly(isobutyl methacrylate), poly (hexyl methacrylate),  
30       poly(isodecyl methacrylate), poly (lauryl methacrylate), poly(phenyl methacrylate), poly (methyl acrylate), poly (isopropyl acrylate), poly (isobutyl actylate), poly (octadecyl acrylate), waxes such as beeswax, carnauba wax, microcrystalline wax, and ozokerite; fatty alcohols

5       such as cetostearyl alcohol, stearyl alcohol; cetyl  
alcohol and myristyl alcohol; and fatty acid esters such  
as   glyceryl monostearate; glycerol monooleate,  
acetylated monoglycerides, tristearin, tripalmitin,  
cetyl esters wax, glyceryl palmitostearate, glyceryl  
10   behenate, glycerol distearate and hydrogenated castor  
oil.

38.A dosage form according to claim 37, wherein the  
hydrophobic release controlling agent(s) is selected  
preferably from ammonio methacrylate co-polymers.

15   39. A dosage form according to claim 38, wherein the  
preferred ammonio methacrylate co-polymers are selected  
from Eudragit RSPO (Ammonio Methacrylate Copolymer type  
B USP), Eudragit RL (Ammonio Methacrylate Copolymer type  
A USP) and Eudragit NE30D (Polyacrylate dispersion 30%  
20   Ph. Eur.).

40. A dosage form according to claim 33, wherein in micro  
matrix particles, the antidiabetic active ingredient and  
one or more hydrophobic release controlling agents are  
present in a ratio of from 100:1 to 100:75.

25   41. A dosage form according to claim 40, wherein in micro  
matrix particles, the antidiabetic active ingredient and  
one or more hydrophobic release controlling agents are  
present preferably in ratio of from 100:2.5 to 100:50.

42. A dosage form according to claim 40, wherein in micro  
30   matrix particles, the antidiabetic active ingredient and  
one or more hydrophobic release controlling agents are  
present more preferably in ratio of from 100:2.5 to  
100:30

- 5 43. A dosage form according to claim 40, wherein in micro matrix particles, the antidiabetic active ingredient and one or more hydrophobic release controlling agents are present most preferably in ratio of from 100:2.5 to 100:20.
- 10 44. A dosage form according to claim 33, wherein coating of micro matrix particles comprises one or more hydrophobic release controlling agents.
45. A dosage form according to claim 44, wherein the hydrophobic release controlling agents are selected from
- 15 the group comprising of ammonio methacrylate copolymers type A and B as described in USP, methacrylic acid copolymer type A, B and C as described in USP, polyacrylate dispersion 30% as described in Ph. Eur., polyvinyl acetate dispersion, ethylcellulose, cellulose acetate, cellulose propionate (lower, medium or higher
- 20 molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, poly(methyl methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate), poly(isobutyl methacrylate), poly (hexyl methacrylate),
- 25 poly(isodecyl methacrylate), poly (lauryl methacrylate), poly(phenyl methacrylate), poly (methyl acrylate), poly (isopropyl acrylate), poly (isobutyl actylate), poly (octadecyl acrylate), waxes such as beeswax, carnauba wax, microcrystalline wax, and ozokerite; fatty alcohols
- 30 such as cetostearyl alcohol, stearyl alcohol; cetyl alcohol and myristyl alcohol; and fatty acid esters such as glyceryl monostearate; glycerol monooleate, acetylated monoglycerides, tristearin, tripalmitin,
- 35 cetyl esters wax, glyceryl palmitostearate, glyceryl

5        behenate, glycerol distearate and hydrogenated castor oil.

46. A dosage form according to claim 45, wherein the hydrophobic release controlling agent(s) is selected from fatty acid esters.

10    47. A dosage form according to claim 46, wherein the hydrophobic release controlling agents are selected from the group comprising of hydrogenated castor oil and glycerol distearate.

15    48. A dosage form according to claim 33, wherein in outer portion, micro matrix particles and coating of one or more hydrophobic release controlling agents are present in a ratio of from 100:0.5 to 100:75.

20    49. A dosage form according to claim 48, wherein in outer portion, micro matrix particles and coating of one or more hydrophobic release controlling agents are present preferably in a ratio of from 100:1 to 100:50.

25    50. A dosage form according to claim 48, wherein in outer portion, micro matrix particles and coating of one or more hydrophobic release controlling agents are more preferably present in a ratio of from 100:2.5 to 100:20.

51. A dosage form according to claim 33, wherein the weight ratio of immediate release antidiabetic active ingredient and modified release antidiabetic active ingredient is from 1:10 to 1:15000

30    52. A dosage form according to claim 33, wherein the low dose antidiabetic active ingredient comprises dose less than or equal to 50 mg.

- 5 53. A dosage form according to claim 33, wherein the low dose  
antidiabetic active ingredient is selected from the  
group comprising of sulphonylurease, meglitinides, PPAR  
gamma agonist [insulin sensitisers (thiazolidinedione)],  
10 alpha-glucosidase inhibitors, PPAR alpha and gamma  
agonist.
54. A dosage form according to claim 33, wherein the low  
dose antidiabetic active ingredient is selected from the  
group comprising of glibenclamide (glyburide), glipizide,  
gliclazide, glimepiride, tolazamide, tolbutamide,  
15 clorpropamide, gliquidone, nateglinide, glyburide,  
glisoxepid, glibornuride, phenbutamide, tolcyclamide,  
repaglinide, troglitazone, ciglitazone, pioglitazone,  
englitazone, acarbose, voglibose, emiglitate, miglitol,  
farglitazar, (S)-2-ethoxy-3-[4-(2-{4-  
20 methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid,  
3-{4-[2-(4- tert-butoxycarbonylaminophenyl)  
ethoxy]phenyl}-(S)-2-ethoxy propanoic acid and  
pharmaceutically acceptable salts thereof.
55. A dosage form according to claim 33, wherein the high  
25 dose high solubility antidiabetic active ingredient is  
selected from biguanides.
56. A dosage form according to claim 33, wherein the high  
dose high solubility antidiabetic active ingredient is  
selected from the group comprising of metformin  
30 hydrochloride, phenformin and buformin
57. A dosage form according to claim 33, wherein the high  
dose high solubility antidiabetic active ingredient  
comprises dose from 500 mg to 1500 mg.

5 58. A dosage form according to claim 33, is once a day oral formulation.

59. A dosage form according to claim 33, is used for human beings.

10 60. A dosage form according to claim 33, wherein the high dose high solubility antidiabetic active ingredient is metformin hydrochloride.

15 61. A dosage form according to claim 33, wherein the composition of outer portion is as follows-

Micro matrix particles-

Metformin hydrochloride	75%w/w to 99%w/w
Eudragit RS	1%w/w to 25%w/w

20 Coated micro matrix particles

Micro matrix particles	70%w/w to 99%w/w
Hydrogenated castor oil	1%w/w to 30%w/w
Magnesium stearate	0%w/w to 2%w/w

25 62. A dosage form according to claim 33, wherein the dissolution of metformin hydrochloride is not more than 50% in one hour, from 30 to 90 % in four hours and not less than 65 % in twelve hours.

30 63. A dosage form according to claim 33, wherein the maximum plasma metformin concentration is achieved between 700 ng/ml and 2500 ng/ml.

- 5 64. A dosage form according to claim 63, wherein the  
maximum plasma metformin concentration is achieved  
preferably between 900 ng/ml and 2400 ng/ml.
65. A dosage form according to claim 63, wherein the maximum  
10 plasma metformin concentration is achieved more  
preferably between 1000 ng/ml and 2350 ng/ml.
66. A dosage form according to claim 33, wherein the  
modified release metformin hydrochloride formulations  
15 for once daily administration exhibit invivo mean  
dissolution time (MDT) of 4 hours to 6 hours.
67. A dosage form according to claim 33, wherein the minimum  
plasma metformin concentration (at 24 hours) ranges  
20 between 0 and 450 ng/ml after oral administration.
68. A dosage form according to claim 33, wherein the low  
dose antidiabetic active ingredient is rosiglitazone  
maleate.
- 25 69. A dosage form according to claim 33, wherein the low  
dose antidiabetic active ingredient is glimepiride.
70. A dosage form as claimed in claim 60 and 68, wherein the  
30 bioavailability of rosiglitazone is not affected when it  
is coadministered with metformin hydrochloride.
71. A dosage form according to claim 33, wherein inner  
portion may optionally contain more than one  
antidiabetic active ingredients.



5 72.A dosage form according to claim 33, wherein outer  
portion may optionally contain more than one  
antidiabetic active ingredients.

73.A process for the preparation of a dosage form as  
claimed in claim 33, comprising a) preparation of inner  
10 portion and b) preparation of outer portion.

74. A process for the preparation of a dosage form as  
claimed in claim 73, wherein preparation of outer  
portion comprising a) preparing a micro matrix particles  
containing high dose, antidiabetic active ingredient and  
15 one or more hydrophobic release controlling agent and  
b) coating the said micro matrix particles containing  
high dose antidiabetic active ingredient and one or more  
hydrophobic release controlling agent.

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